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Adenocarcinoma *in situ* (ductal type) ex pleomorphic adenoma of the lacrimal gland

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ABSTRACT

Purpose: To present the clinical and histopathological characteristics of a rare case of ductal carcinoma *in situ* ex pleomorphic adenoma in the lacrimal gland.

Observations: A 73-years-old Caucasian female presented with complaints of double vision and pain in the left eye region. Clinical examination revealed ptosis and exophthalmos of the left eye as well as diplopia on downward gaze. Magnetic resonance imaging of the left orbit demonstrated a 17 × 22 mm homogeneous tumor in the left lacrimal fossa. The tumor was excised *in toto*. Histopathological examination revealed a pleomorphic adenoma with ductal structures with benign looking epithelial cells, surrounded by myoepithelial cells. Tumor areas with cribriform architecture consisting of ductal structures with abnormal luminal epithelial cells and intact myoepithelial cell layer were also present. The surgical margins were clear. All luminal and myoepithelial cells were positive for cytokeratin 7, the luminal cells in the cribriform areas were positive for human epidermal growth factor 2 and androgen receptor. The myoepithelial cells were positive for cytokeratin 5, calponin and focally for glial fibrillar acid protein. The findings were diagnostic for ductal carcinoma *in situ* ex pleomorphic adenoma. Next generation sequencing Oncomine Comprehensive Assay mutation analysis found mutations in the BRCA2 (p.K3326*), BAP1 (p.S395*), and TP53 (p.E285K) genes in the ductal carcinoma *in situ* and BRCA2 (p.C9976A) in the pleomorphic adenoma part.

Conclusion and importance: To our knowledge, this tumor is only the second described ductal carcinoma *in situ* ex pleomorphic adenoma of the lacrimal gland.

1. Introduction

Tumors of the lacrimal gland are rare and represent around 12% of all orbital tumors.[1] The most common type is of epithelial origin and accounts approximately for 20% of all biopsied cases.[2] Of these epithelial lesions, approximately 50% are pleomorphic adenoma (PA).[3] PA is a benign mixed tumor comprised of both epithelial and mesenchymal-like tissues.[4] Though rare, these tumors have a tendency to recur or undergo a malignant transformation, carcinoma ex PA.[5] Furthermore, these tumors may show morphological variations, where the most common type is ductal carcinoma.[6] Ductal carcinoma of the lacrimal gland resembles salivary duct carcinoma in both immunohistochemical profile and mutational pattern as well as ductal carcinoma of the breast, as first described by Katz et al. (1996).[7] Here, we present the clinical and histopathological characteristics of a rare case on ductal carcinoma *in situ* (CIS) ex PA.

2. Case report

A 73-year-old Caucasian female presented with complaints of double vision and ptosis of the left eye three months prior to the clinical examination. Furthermore, she reported pain from the left eye for the past three days. The patient had a past medical history of congestive heart failure, cardiac ablation due to paroxysmal supraventricular tachycardia and hydronephrosis.

Clinical examination revealed ptosis and exophthalmos of the left eye as well as diplopia on downward gaze. There was two-millimetre proptosis and restricted eye motility in all directions of the left eye. Visual acuity was normal on both eyes. Magnetic resonance imaging (MRI) of the orbit demonstrated a 17 × 22 mm homogeneous tumor with

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an area of calcification in the left lacrimal fossa and showed no signs of invasion of the surrounding structures (Fig. 1A and B). Seven years prior to the examination, an orbital MRI was performed of the patient due to clinical suspicion of an acoustic neuroma. However, a tumor in the left lacrimal fossa was overlooked and the orbital MRI was therefore described as normal. A comparison of the two MRIs showed that the tumor was present on the earlier MRI (7 years prior), but there was no change in shape nor in size over the interval. The patient underwent excision of an intracapsular tumor (sized 20 × 15 × 12 mm) via lateral orbitotomy with a preoperative tentative diagnosis of a PA. The tumor did not involve the orbital bones nor the capsule. At 6 months follow-up, the patient showed no signs of recurrence by a control MRI.

Formalin-fixed paraffin-embedded (FFPE) tissue from the resected orbital tumor was stained with hematoxylin and eosin and periodic acid-Schiff (PAS).

Immunohistochemical staining of 4 μm sections were performed using the following antibodies: Ki-67, cytokeratin 5 (CK5), cytokeratin 7 (CK 7), human epidermal growth factor 2 (HER2), calponin, glial fibrillar acid protein (GFAP) and androgen receptor (AR).

The tissue was macro dissected guided by an HE-stained section to enrich tumor cells in the downstream analyses. Tumor deoxyribonucleic acid (DNA) was extracted from FFPE tissue blocks using an in-house raw extraction method (Proteinase K and Tris EDTA). The sequencing library was prepared using Oncomine Comprehensive Assay version 3 (Thermo Fischer Scientific, Waltham, Massachusetts, USA) targeting 161 cancer-related genes. The library was sequenced on the Ion S5 platform (Thermo Fischer). Tumor ribonucleic acid (RNA) was also extracted and fusion analysis was performed using the Archer Fusionplex Expanded Sarcoma panel.

The tumor showed areas with typical PA consisting of normal looking ductal structures with benign looking epithelial cells surrounded by myoepithelial cells (Fig. 1C). Moreover, areas with dense extracellular matrix with fibrosis were also observed (Fig. 1C).

However, minor areas with epithelial cells showing signs of malignancy in the form of pleomorphic nuclei and frequent mitotic figures (Fig. 1E) were present too. Furthermore, areas with duct structure showing characteristics of "Roman bridges" with a pleomorphic lining were also present (Fig. 1F). The luminal cells were surrounded by myoepithelial cells highlighted by CK5-staining (Fig. 1D). The surgical margins were clear.

Immunohistochemical staining showed all luminal and myoepithelial cells being positive for CK7, and the carcinoma *in situ* component was additionally positive for HER2 and AR. The myoepithelial cells were positive for CK5, calponin and focally for GFAP. Ki-67 revealed a proliferative activity of 20% in the carcinoma *in situ* component. The findings were diagnostic for ductal CIS ex PA.

Next generation sequencing Oncomine Comprehensive Assay mutation analysis found mutations in the *BRCA2* (p.K3326*), *BAP1* (p.S395*), and *TP53* (p.E285K) genes in the ductal CIS ex PA part (Fig. 1G) and BRCA2 (p.C9976A) in the PA part.

CARMN-PLAG1 (chr5:148786641, chr8:57083748) fusion was detected in the ductal CIS ex PA part and CARMN-PLAG1 (chr5:148786641, chr8:57083748) and CARMN-PLAG1 (chr5:148786641, chr8:57092072) fusions were detected in the PA part using the Archer Fusionplex Expanded Sarcoma panel.

3. Discussion

PAs of the lacrimal gland are usually slow growing tumors, most commonly presented in the 5th and 6th decade, with a mean age at diagnosis of 48 years reported in a large survey.[8] There seems not to be a male or female predominance. Patients show one or more symptoms relating to a growing tumor at the site of the lacrimal gland like eyeball displacement, proptosis, decreased motility, diplopia, and ptosis.[9]

Carcinoma ex PA refers to a malignant tumor that arises from a pre-existing benign pleomorphic adenoma. The recent WHO definition of this condition specifies that the carcinoma must be histologically distinct from the benign component, and that the malignant component must have invaded through the capsule of the original pleomorphic adenoma.[4] The malignant histological subtypes include adenocarcinoma NOS or salivary duct carcinoma, the latter being the most common type. Other types include myoepithelial carcinoma, which accounts for 35% of the cases and the rare types include adenoid cystic carcinoma.[4] Salivary duct carcinoma shares histological findings that resembles that of invasive ductal carcinoma of the breast including a hyalinized, fibrous stroma infiltrated by neoplastic ducts.[10] CIS ex PA is a non-invasive type which is usually found in the lacrimal glands and small salivary glands. A similar type of non-invasive carcinoma is seen in the breast and is called ductal CIS. In ductal breast CIS, there is a growth of abnormal cells in the mammary ducts that does not invade the basement membrane.[11] The diagnostic clue in most cases relies on an intraductal component comprising proliferating luminal cells with varying degrees of nuclear pleomorphism. These cells can form structures like "Roman-bridges," cribriform and papillary architecture, and can show central comedonecrosis.[12] Furthermore, CK5 staining is used as a biological marker to determine the risk of progression to invasive disease, which is commonly positively expressed in CIS.[13] This shows that the myoepithelial cell layer is intact and that there is no sign of stromal invasion. These histologic features were found in our case in addition to that the capsule was intact; therefore, the tumor was classified as intracapsular CIS ex pleomorphic adenoma of ductal type.

By reviewing the literature, we found three reports that described adenocarcinoma *in situ* not otherwise specified (NOS) in the lacrimal gland[14–16] and only one report, which is the most recent, describes high-grade ductal CIS ex PA of the lacrimal gland[17] similar to our case findings. In the latter case by Garakani et al.[17] "Roman-bridge" configuration that defines the ductal structures in adenocarcinoma was also demonstrated. The most common symptoms present were exophthalmos and diplopia[14–16] as our current case, besides from one case where the only symptom was acute vertigo.[17] Only in the most recent case report, immunohistochemical staining was performed demonstrating positive staining for HER2 and AR in the CIS ex PA component as well as increased Ki-67 index,[17] similarly to the present case. This can also be compared to ductal carcinoma of the breast in addition to salivary duct carcinoma that share similar immunohistochemical profiles for AR, Ki-67 and HER2 among others.[18,19] On the other hand, our case is the first investigating mutational analysis of the tumor, which resulted in gene mutations located to *BRCA2*, *BAP1* and *TP53*.

The tumor suppressor gene, *BRCA2*, is found in hereditary breast cancer.[20] A small percentage of the remaining forms of hereditary breast cancer are due to mutations in the genes *TP53*. Carriers of *BRCA2* genes mutations are likely to be present with ductal CIS.[21] On the other hand, the *BAP1* has not shown to be a high-risk breast cancer predisposing gene.[22] The mutations found in our case show similarities with ductal CIS in breast cancer as well as carcinoma ex PA of the salivary gland.[23,24] Moreover, both the CIS component and the pleomorphic adenoma were CARMN-PLAG1 positive in the present case. An explanation could be that the CIS component has developed from the CARMN-PLAG1 positive pleomorphic adenoma.

Surgical excision is the most used method to treat PA of the lacrimal gland. Incompletely excised tumors may show relapse, and in some cases progression to carcinoma ex PA of the lacrimal gland.[25] Multiple recurrences may increase the risk of malignant transformation as seen with its counterpart PA of the salivary glands.[26] The prognosis is therefore good when the tumor is completely excised and there is no extension beyond the capsule.

4. Conclusion

To our knowledge, this tumor is the second case described on ductal CIS ex PA. However, the present case is the only so far that includes mutational analysis which shows comparable histological features and

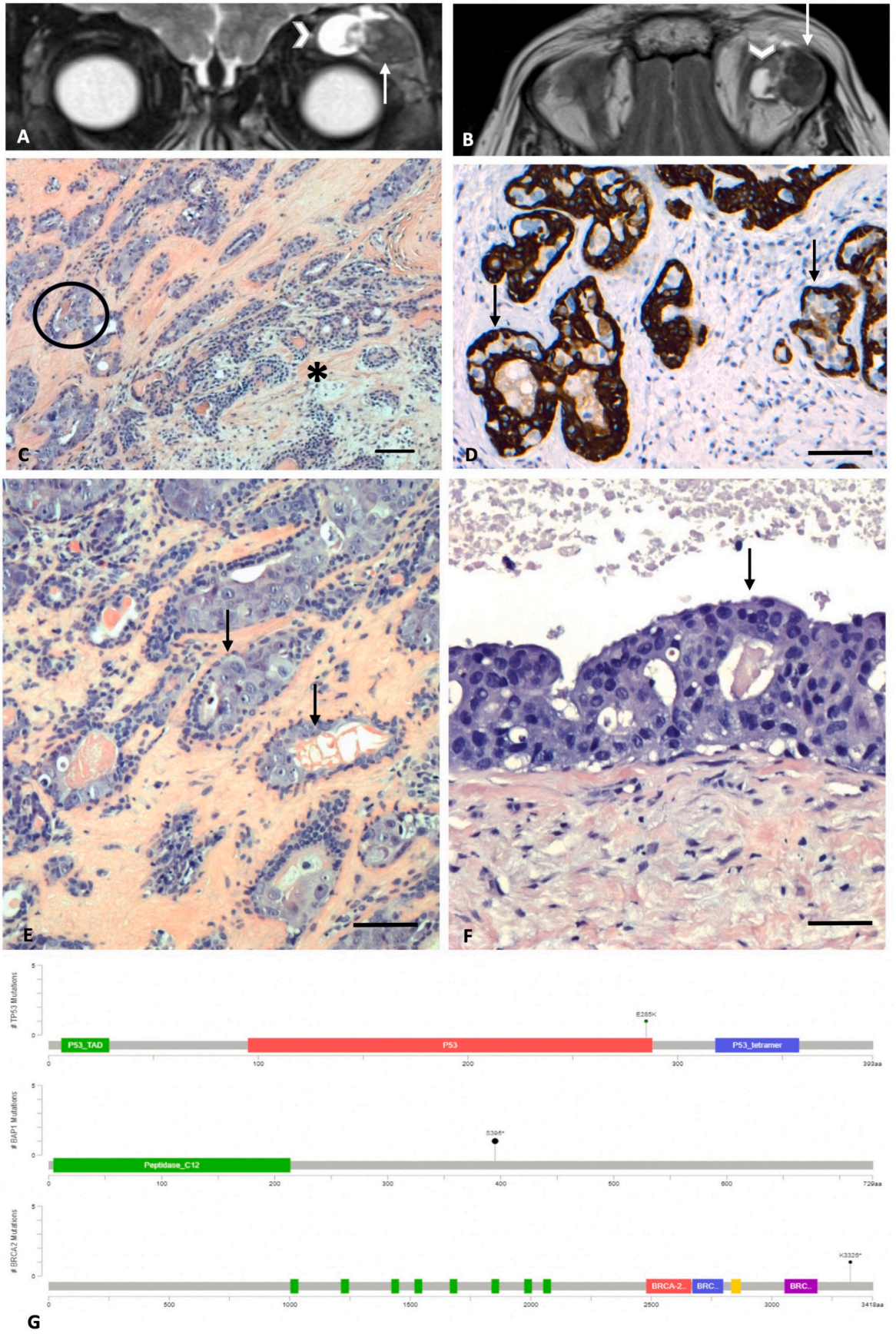

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Fig. 1. A: Magnetic resonance imaging (coronal view) of both orbits illustrates a 17 mm × 22 mm round tumor (arrow) in the left orbit with downwards displacement of the eye. Calcifications is seen on the right side of the tumor (arrowhead).
B: In axial view (calcifications (arrowhead)).
C: Ducts with *in situ* carcinoma (circle). Pleomorphic adenoma in the right lower corner (asterisk) (bar = 100 μm).
D: Cytokeratin 5 staining displaying intact myoepithelial cells (arrows) surrounding the abnormal ductal epithelial cells. There are no signs of stromal invasion (bar = 50 μm).
E: Carcinoma *in situ* changes of the ductal structures lined by abnormal ductal epithelial cells (arrows) (bar = 50 μm).
F: Duct structure shows characteristics of "Roman bridges" (arrow) with a pleomorphic lining (bar = 250 μm).
G: A lollipop diagram depicting mutations of the *BAP1*, *TP53* and *BRCA2* genes in the ductal CIS part.

genetic mutations as presented in ductal CIS of the breast. The treatment was surgical excision with no sign of recurrence at 6 months follow-up.

Patient consent

The patient consented to publication of the case. This case report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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